Report from the Gastrointestinal Cancers Symposium

Carcinoid and pancreatic neuroendocrine tumours

CABOZANTINIB

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TRIAL SUMMARY: Results of a phase II trial

Chan JA, Faris JE, Murphy JE, et al. Phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumours (pNET). *J Clin Oncol* 35, 2017 (Suppl 4S; abstract 228).

Activation of the tyrosine kinase receptors, vascular endothelial growth factor receptor (VEGFR)-2 and c-MET, plays a role in the growth of neuroendocrine tumours (NETs). Expression of c-MET has been associated with shorter survival. Cabozantinib has been shown to inhibit VEGFR-2 and c-MET and is approved for the treatment of renal cell carcinoma (RCC). This 2 cohort phase 2 study evaluates the efficacy of cabozantinib in patients with progressive, well-differentiated, grade 1 or 2 unresectable or metastatic carcinoid tumours (n=41) or pNETs (n=20). There was no limit to prior therapy. Patients were treated with cabozantinib 60 mg po qd, with dose reduction to 20 or 40 mg once daily required in 81% of the 53 patients who completed more than 1 cycle of treatment. The primary endpoint was objective response rate (ORR) as measured by RECIST (Response Evaluation Criteria In Solid Tumors) 1.1.

Results: Three of the 20 patients with pNET achieved partial response (PR) (ORR 15%, 95% CI: 5–36%); 15 had stable disease. six of the 41 patients with carcinoid achieved PR (ORR 15%, 95% CI: 7–28%); 26 had stable disease. Reported median progression-free survival (PFS) was 21.8 months (95% CI: 8.5–32.0 months) in patients with pNET and 31.4 months (95% CI: 8.5 months NR) in patients with carcinoid NETs. Grade 3/4 toxicities included hypertension (13%), hypophosphatemia (11%), diarrhea (10%), lymphopenia (7%), thrombocytopenia (5%), fatigue (5%), and increased lipase or amylase (8%). One patient developed heart failure and 1 patient had autoimmune hemolytic anemia. Treatment with cabozantinib was associated with objective tumour responses and encouraging PFS durations in patients with advanced carcinoid and advanced pNET. Further evaluation of cabozantinib is warranted in both NET subgroups.

COMMENTARY: It is known that expression of c-MET in neuroendocrine tumours results in a higher rate of recurrence and shorter survival. A number of trials confirm that simultaneous inhibition of VEGF and c-MET signalling pathways slows down tumour growth and reduces invasion and metastasis.[1] This 2-cohort phase 2 study investigates the role of dual inhibitor cabozantinib in pretreated patients with well-differentiated grade 1 or 2 unresectable or metastatic carcinoid or pancreatic NETs. The median number of previous lines of treatment was 3 in pNETs and 1 in the carcinoid cohort. Ninety per cent of patients with pNETs had either partial response or stable disease, as did 78% of patients with carcinoid. Reported PFS was 21.8 months in patients with pNETs and 31.4 months for patients with carcinoid tumours. These are significantly longer than the duration of PFS and time to progression (TTP) seen with conventional treatment, such as sunitinib (10.2 months), pazopanib (12.7 months), everolimus (63 weeks), and bevacizumab (66 weeks).[2,3] Adverse effects of treatment that required dose reduction and/or treatment discontinuation were the same as reported in earlier studies of cabozantinib: hypertension (13%), hypophosphatemia (11%), diarrhea (10%), lymphopenia (7%), thrombocytopenia (5%), fatigue (5%), and increased lipase or amylase (8%). It remains to be determined whether ORR and PFS translate into improvements in overall survival.

IN BRIEF

Already known

- Cabozantinib has been shown to inhibit VEGFR-2 and c-MET and is approved for the treatment of renal cell carcinoma.
- Expression of c-MET in neuroendocrine tumours results in a higher rate of recurrence and shorter survival.

What this study showed

- This phase 2 trial found that cabozantinib was associated with objective tumour responses and encouraging progression-free survival (PFS) in patients with advanced carcinoid and advanced pancreatic neuroendocrine tumours (pNETs).

Next steps

- Conduct further evaluation in both subgroups.